SUPPLEMENTARY INFORMATION

Structure-based design, synthesis and evaluation *in vitro* of arylnaphthyridinones, arylpyridopyrimidinones and their tetrahydro derivatives as inhibitors of the tankyrases

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Contents

Chemistry experimental

1-Iodo-4-phenylmethoxybenzene (19h). BnBr (389 mg, 4.7 mmol) was added to **19i** (1.00 g, 4.6 mmol) and Cs_2CO_3 (1.50 g, 4.6 mmol) in dry DMF (10 mL) and the mixture was stirred for 90 min. The mixture was diluted with water (10 mL) and extracted thrice with EtOAc. The combined extracts were washed (water, brine). Drying and chromatography (petroleum ether / EtOAc, 99:1) gave **19h** (1.20 g, 82%) as white crystals: mp 59-61°C (lit.[1] mp 56.5-57°C); IR ν_{max} 1582 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.99 (2 H, s, CH_2), 6.76 (2 H, d, J = 9.0 Hz, 3,5-H_2), 7.31-7.43 (5 H, m, Ph 2,3,4,5,6-H_5), 7.56 (2 H, d, J = 9.0 Hz, 2,6-H_2); ^{13}C NMR ($CDCl_3$) δ 70.06 (CH_2), 83.01 (4-C), 117.29 (2,6-C_2), 127.37 (Ph 3,5-C_2), 128.06 (Ph 4-C), 128.59 (Ph 2,6-C_2), 136.50 (Ph 1-C), 138.21 (3,5-C_2), 158.61 (1-C).

4-Methoxy-1-trimethylsilylethynylbenzene (20c). Et_3N (10 mL) and THF (10 mL) were added to 4-methoxyiodobenzene **19c** (1.05 g, 4.5 mmol), CuI (87 mg, 450 μmol), $(Ph_3P)_2PdCl_2$ (158 mg, 225 μmol) and Na ascorbate (89 mg, 450 μmol) under Ar. The mixture was stirred at 40°C for 30 min. $Me_3SiC{\equiv}CH$ (1.03 g, 10.5 mmol) was added and the mixture was stirred at 40°C for 16 h. The evaporation residue, in CH_2Cl_2, was washed (water, 2 ×) and dried. Chromatography (petroleum ether / EtOAc 99:1) gave **20c** (909 mg, 99%) as an oil (lit.[2] oil): ^1H NMR ($CDCl_3$) δ 0.23 (9 H, s, $SiMe_3$), 3.79 (3 H, s, OMe), 6.80 (2 H, d, J = 6.8 Hz, 3,5-H_2), 7.40 (2 H, d, J = 4.9 Hz, 2,6-H_2); ^{13}C NMR ($CDCl_3$) δ -0.002 ($SiMe_3$), 55.17 (OMe), 92.34 (ethyne 1-C), 105.15 (ethyne 2-C), 113.75 (2,6-C_2), 115.25 (4-C), 133.39 (3,5-C_2), 159.70 (1-C); MS *m/z* 205.1037 $(M + H)^+$ ($C_{12}H_{17}OSi$ requires 205.1049).

4-Trifluoromethyl-1-trimethylsilylethynylbenzene (20d). 4-Trifluoromethyl-1-iodobenzene **19d** was treated with CuI, $(Ph_3P)_2PdCl_2$, Na ascorbate and $Me_3SiC{\equiv}CH$ in THF and Et_3N, as for the synthesis of **20c**, to give **20d** (92%) as a colourless oil (lit.[3] oil): IR ν_{max} 2161, 2063, 1614, 1511, 1323 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.27 (9 H, s, $SiMe_3$), 7.54 (4 H, s, 2,3,5,6- H_4); ^{13}C NMR ($CDCl_3$) δ -0.02 ($SiMe_3$), 88.07 (ethyne 2-C), 97.13 (ethyne 1-C), 123.90 (q, J = 272 Hz, CF_3), 125.13 (q, J = 3.9 Hz, 3,5-C_2), 126.99 (q, J = 1.4 Hz, 1-C), 130.19 (q, J = 32.7 Hz, 4-C), 132.17 (2,6-C_2); ^{19}F NMR ($CDCl_3$) δ -62.94 (s, CF_3).

4-Chloro-1-trimethylsilylethynylbenzene (20e). 4-Chloroiodobenzene **19e** was treated with CuI, $(Ph_3P)_2PdCl_2$, Na ascorbate and $Me_3SiC{\equiv}CH$ in THF and Et_3N, as for the synthesis of **20c**, to give **20e** (96%) as a pale buff powder: mp 42-45°C (lit.[4] mp 43-45°C); IR ν_{max} 2157, 1643, 1588, 825, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.24 (9 H, s, $SiMe_3$), 7.26 (2 H, d, J = 8.8 Hz, 2,6-C_2), 7.37 (2 H, d, J = 8.9 Hz, 3,5-C_2); ^{13}C NMR ($CDCl_3$) δ 0.00 ($SiMe_3$), 95.47 (ethyne 2-C), 121.78 (ethyne 1-C), 115.08 (4-C), 128.65 (2,6-C_2), 133.29 (3,5-C_2), 134.62 (1-C).

1-Amino-4-trimethylsilylethynylbenzene (20g). 4-Iodoaniline **19g** was treated with CuI, $(Ph_3P)_2PdCl_2$, Na ascorbate and $Me_3SiC{\equiv}CH$ in THF and Et_3N, as for the synthesis of **20c**, to give **20g** (74%) as an off-white solid: mp 94-98°C (lit.[5] mp 93-95°C); IR ν_{max} 3467, 2158, 1622, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.22 (9 H, s, $SiMe_3$), 3.77 (2 H, br, NH_2), 6.56 (2 H, d, J = 8.6 Hz, 2,6-H_2), 7.27 (2 H, d, J = 8.2 Hz, 3,5-H_2); ^{13}C NMR ($CDCl_3$) δ -0.002 ($SiMe_3$), 91.22 (ethyne 2-C), 105.86 (ethyne 1-C), 112.45 (4-C), 114.38 (2,6-C_2), 133.24 (3,5-C_2), 146.63 (1-C).

(4-Phenylmethoxyoxyphenylethynyl)trimethylsilane (20h). Compound **19h** was treated with CuI, $(Ph_3P)_2PdCl_2$, Na ascorbate and $Me_3SiC{\equiv}CH$ in THF and Et_3N, as for the synthesis of **20c**, to give **20h** (92%) as a white solid: mp 45-47°C (lit.[6] mp 50°C); IR ν_{max} 2157, 1602

cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.25 (9 H, s, $SiMe_3$), 5.06 (2 H, s, CH_2), 6.89 (2 H, d, J = 6.8 Hz, 3,5-H_2), 7.25-7.40 (7 H, m, 2,6-H_2, Ph 2,3,4,5,6-H_5); ^{13}C NMR ($CDCl_3$) δ -0.002 ($SiMe_3$), 69.96 (CH_2), 92.50 (ethyne 2-C), 105.09 (ethyne 1-C), 114.71 (3,5-C_2), 115.25 (1-C), 127.39 (Ph 2,6-C_2), 128.01 (Ph 4-C), 128.55 (Ph 3,5-C_2), 133.42 (2,6-C_2), 136.54 (Ph 1-C), 158.87 (4-C).

4-(Trimethylsilylethynyl)pyridine (20l). CuI (95 mg, 0.50 mmol), $(Ph_3P)_2PdCl_2$ **3** (174 mg, 0.25 mmol), Na ascorbate (98 mg, 0.50 mmol) and 4-bromopyridine hydrochloride **22** (970 mg, 5.0 mmol) were placed in a flask, which was degassed and filled with Ar. Pr^i_2NH (10 mL) and THF (10 mL) were added. The mixture was stirred at 40°C for 30 min. $Me_3SiC{\equiv}CH$ (532 mg, 5.0 mmol) was added and the mixture was stirred at 40°C for 10 h. Evaporation and chromatography (petroleum ether / EtOAc 5:1 → 3:1) gave **20l** (767 mg, 89%) as a pale buff oil (lit.[7] yellow liquid); ^1H NMR ($CDCl_3$) δ 0.27 (9 H, s, $SiMe_3$), 7.29 (2 H, d, J = 4.4 Hz, 3,5-H_2) 8.55 (2 H, d, J = 4.4 Hz, 2,6-H_2); ^{13}C NMR ($CDCl_3$) δ -0.002 ($SiMe_3$), 100.24 (ethyne 2-C), 102.31 (ethyne 1-C), 126.16 (3,5-C_2), 131.52 (4-C), 150.03 (2,6-C_2).

1-Ethynyl-4-methoxybenzene (21c). Compound **20c** (1.00 g, 4.9 mmol) in THF (100 mL) was stirred with Bu_4NF in THF (1.0 M, 10 mL) for 16 h. Saturated aq. $NaHCO_3$ was added and the mixture was extracted (Et_2O, 3 ×). Drying and chromatography (petroleum ether / EtOAc 19:1) gave **21c** (595 mg, 92%) as a pale yellow oil (lit.[8] oil): IR ν_{max} 2158, 1607, 1570, 1507 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.98 (1 H, s, C≡CH), 3.80 (3 H, s, Me), 6.83 (2 H, d, J = 9.5 Hz, 3,5-H_2), 7.42 (2 H, d, J = 9.4 Hz, 2,6-H_2); ^{13}C NMR ($CDCl_3$) δ 55.20 (OMe), 67.89 (ethyne 2-C), 83.60 (ethyne 1-C), 113.88 (2,6-C_2), 114.14 (4-C), 133.52 (3,5-C_2), 159.90 (1-C).

1-Ethynyl-4-trifluoromethylbenzene (21d). Compound **20d** was treated with Bu_4NF, as for the synthesis of **21c**, to give **21d** (66%) as a colourless oil (lit.[9] oil): IR ν_{max} 1519, 1323 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.18 (1 H, s, C≡CH), 7.58 (4 H, s, 2,3,5,6-H_4), ^{13}C NMR ($CDCl_3$) δ 79.51 (ethyne 2-C), 82.13 (ethyne 1-C), 123.81 (q, J = 288 Hz, CF_3), 125.24 (2,6-C_2), 125.88 (4-C), 130.57 (q, J = 33 Hz, 4-C), 132.33 (3,5-C_2); ^{19}F NMR ($CDCl_3$) δ -62.96 (s, CF_3).

1-Chloro-4-ethynylbenzene (21e). Compound **20e** was treated with Bu_4NF, as for the synthesis of **21c**, to give **21e** (57%) as a pale amber powder: mp 41-44°C (lit.[10] mp 43-44.5°C): IR ν_{max} 2154, 1645, 1589, 1488, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.09 (1 H, s, C≡CH), 7.29 (2 H, d, J = 8.8 Hz, 3,5-H_2), 7.41 (2 H, d, J = 8.9 Hz, 2,6-H_2); ^{13}C NMR ($CDCl_3$) δ 78.07 (ethyne 2-C), 85.45 (ethyne 1-C), 120.55 (4-C), 128.61 (3,5-C_2), 133.28 (2,6-C_2), 134.86 (1-C).

1-Amino-4-ethynylbenzene (21g). Compound **20g** (423 mg, 2.2 mmol) in THF (100 mL) was stirred with Bu_4NF in THF (1.0 M, 6.7 mL) for 16 h at 35°C. Saturated aq. $NaHCO_3$ was added. The mixture was extracted (Et_2O, 3 ×). Drying and chromatography (petroleum ether / EtOAc 1:3) gave **21g** (230 mg, 81%) as a pale green powder: mp 81-85°C (lit.[11] mp 88-90°C): IR ν_{max} 3486, 3388, 2095, 1619, 1513 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.95 (1 H, s, C≡CH), 3.79 (2 H, s, NH_2), 6.58 (2 H, d, J = 7.6 Hz, 2,6-H_2), 7.28 (2 H, d, J = 7.7 Hz, 3,5-H_2); ^{13}C NMR ($CDCl_3$) δ 74.79 (ethyne 2-C), 84.32 (ethyne 1-C), 111.34 (4-C), 114.52 (2,6-C_2), 133.41 (3,5-C_2), 146.95 (1-C).

4-Ethynylpyridine (21l). Compound **20l** (2.30 g, 13.1 mmol) in THF (30 mL) was stirred at 40°C with Bu_4NF in THF (1.0 M, 30 mL) for 10 h. Sat. aq. $NaHCO_3$ was added and the mixture was extracted (EtOAc, 3 ×). Drying, evaporation and chromatography (petroleum ether / EtOAc 3:1) gave **21l** (550 mg, 42%) as an off-white powder with a strong unpleasant

odour: mp 51-54°C (lit.[12] 62-63°C); IR ν_{max} 3378, 1641, 1594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.28 (1 H, s, C≡CH), 7.33 (2 H, d, *J* = 5.8 Hz, 3,5-H_2), 8.59 (2 H, m, 2,6-H_2); ^{13}C NMR ($CDCl_3$) δ 60.29 (ethyne 1-C), 80.88 (ethyne 2-C), 126.16 (3,5-C_2), 130.25 (4-C), 149.74 (2,6-C_2).

2-Bromo-3-cyanopyridine (24). 2-Chloro-3-cyanopyridine **23** (3.68 mg, 26 mmol) was boiled under reflux with AcOH (100 mL) for 12 h. The evaporation residue, in THF (80 mL) and H_2O (20 mL), was boiled under reflux for 4 h. Evaporation gave 3-cyanopyridin-2-one (3.12 g, quant.) as white crystals: mp 110-114°C (lit.[13] 174-175°C); ^1H NMR δ 6.47 (1 H, t, *J* = 6.6 Hz, 5-H), 7.91 (1 H, dd, *J* = 6.5, 2.1 Hz, 4-H), 8.14 (1 H, dd, *J* = 7.0, 2.1 Hz, 6-H), 11.48 (1 H, s, 1-H); ^{13}C NMR δ 105.80 (3-C), 124.05 (5-C), 141.87 (CN), 144.50 (6-H), 150.02 (4-C), 154.20 (2-C); MS *m/z* 143.0214 $(M + Na)^+$ ($C_6H_4N_2NaO$ requires 143.0222). Bu_4NBr (8.55 g, 26 mmol) and P_2O_5 (3.67 g, 26 mmol) were heated in PhMe (250 mL) at 80°C for 30 min. The above 3-cyanopyridin-2-one (1.59 g, 13 mmol) was added and the mixture was boiled under reflux for 12 h. The mixture was cooled, poured into cold water and extracted (EtOAc, 2 ×). Drying and evaporation gave **24** (2.24 g, 94%) as off-white crystals: mp 114-118°C (lit.[14] mp 105°C); IR ν_{max} 2236, 1574, 1550, 1472 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42 (1 H, dd, *J* = 7.7, 4.8 Hz, 5-H), 8.01 (1 H, dd, *J* = 7.8, 2.0 Hz, 4-H), 8.57 (1 H, dd, *J* = 4.9, 2.0 Hz, 6-H); ^{13}C NMR δ 114.27 (3-C), 115.63 (CN), 122.37 (5-C), 142.53 (4-C), 143.84 (2-C), 152.92 (6-C).

3-Bromopyridine-4-carboxylic acid (31). 3-Bromopyridine **30** (164 mg, 1.0 mmol) was added to $LiNPr^i_2$ in dry THF (1.0 M, 15 mL, 1.5 mmol) and the mixture was stirred at -78°C for 30 min under Ar. Crushed solid CO_2 was added under Ar, and the cooling was removed. The mixture was stirred until reaching 20°C. Water (10 mL) was added. The organic solvents were evaporated. The solution was washed thrice with Et_2O. Aq. HCl (9 M) was added to pH 3. The mixture was stirred for 1 h and extracted (EtOAc, 3 ×). The combined extracts were washed (brine) and dried. Evaporation gave **31** (20 mg, 10%) as white needles: mp 175-176ºC (decomp.) (lit.[15] mp 240°C); ^1H NMR δ 7.71 (1 H, d, *J* = 4.8 Hz, 6-H), 8.70 (1 H, d, *J* = 4.9 Hz, 5-H), 8.91 (1 H, s, 2-H) 12.56 (1 H, br, OH); ^{13}C NMR ($CDCl_3$) δ 117.26 (4-C), 123.77 (6-C), 148.94 (5-C), 152.61 (2-C), 165.00 (C=O), 166.07 (3-C); MS *m/z* 202 / 200 $(M - H)^-$.

3-Bromopyridine-4-carboxamide (32) and ethyl 3-bromopyridine-4-carboxylate (33). EtO_2CCl (0.58 g, 5.4 mmol) was added dropwise to an ice-cold mixture of **31** (1.00 g, 4.6 mmol), dry THF (15 mL) and dry Et_3N (1.0 mL). The mixture was stirred for 1 h at 0ºC, then NH_3 was bubbled through the suspension for 15 min. The mixture was filtered. The solids were washed with hot Me_2CO. The solvent was evaporated from the combined filtrate and washings. Recrystallisation (EtOH) gave **32** as an off-white powder (777 mg, 78%): mp 149-150ºC; ^1H NMR ($CDCl_3$) δ 7.48 (1 H, d, *J* = 4.8 Hz, 5-H), 7.88 (1 H, br, NH), 8.11 (1 H, br, NH), 8.65 (1 H, d, *J* = 4.8 Hz, 6-H), 8.84 (1 H, s, 2-H); ^{13}C NMR ($CDCl_3$) δ 116.82 (3-C), 122.73 (5-C), 146.02 (4-C), 148.58 (6-C), 151.68 (2-C), 167.03 (C=O); MS *m/z* 224.9469 $(M + Na)^+$ ($C_6H_5{}^{81}BrN_2NaO$ requires 224.9457), 222.9485 $(M + Na)^+$ ($C_6H_5{}^{79}BrN_2NaO$ requires 222.9477). Evaporation of the solvent from the mother liquor gave **33** (60 mg, 5%) as a yellow liquid: ^1H NMR ($CDCl_3$) δ 1.41 (3 H, t, *J* = 7.2 Hz, Me), 4.43 (2 H, q, *J* = 7.3 Hz, CH_2), 7.59 (1 H, d, *J* = 4.9 Hz, 5-H), 8.59 (1 H, d, *J* = 4.9 Hz, 6-H), 8.83 (1 H, s, 2-H); ^{13}C NMR ($CDCl_3$) δ 14.04 (Me), 62.33 (CH_2), 118.71 (3-C), 124.15 (5-C), 139.34 (4-C), 148.41 (6-C), 153.64 (2-C), 164.47 (C=O); MS *m/z* 253.9623 $(M + Na)^+$ ($C_8H_8{}^{81}BrNNaO_2$ requires 253.9611), 251.9638 $(M + Na)^+$ ($C_8H_8{}^{79}BrNNaO_2$ requires 251.9631), 224.9469 $(M + H)^+$ ($C_6H_5{}^{81}BrN_2O$ requires 224.9457), 222.9485 $(M + H)^+$ ($C_6H_5{}^{79}BrN_2O$ requires 222.9477).

3-Bromo-4-cyanopyridine (34). Compound **32** (687 mg, 3.4 mmol) was stirred at reflux with $POCl_3$ (5.0 mL) for 2 h. The mixture was cooled, poured onto ice (100 g) and neutralised with aq. NaOH (5 M, 60 mL). The mixture was extracted Et_2O (2 ×). The combined extracts were washed (sat. aq. $NaHCO_3$), treated with charcoal and filtered. Evaporation and recrystallisation (petroleum ether) gave **34** as an off-white powder (292 mg, 42%): mp 79-81ºC (lit.[16] mp 96.6-98.2ºC); ^{1}H NMR ($CDCl_3$) δ 7.53 (1 H, d, J = 4.9 Hz, 5-H), 8.69 (1 H, d, J = 4.9 Hz, 6-H), 8.92 (1 H, s, 2-H); ^{13}C NMR ($CDCl_3$) δ 114.79 (C≡N), 122.14 (4-C), 124.17 (3-C), 126.75 (5-C), 148.76 (6-C), 152.69 (2-C); MS *m/z* 182.9541 $(M + H)^+$ ($C_6H_4N_2{}^{79}Br$ requires 182.9552).

1,3-Bis(4-methylphenyl)propane-1,3-dione (37b). NaH (2.00 g, 50 mmol, 60% in oil) was washed free from oil with dry hexane (10 mL) at 0ºC under Ar. Dry THF (30 mL) was added, followed by methyl 4-methylbenzoate (3.30 g, 22 mmol) in dry THF (10 mL) and 4-methyl-1-acetylbenzene (2.66 g, 20 mmol) in dry THF (10 mL) at 0ºC under Ar. The suspension was stirred under reflux for 16 h. The mixture was cooled and filtered (Celite®). The solid was washed with EtOH (20 mL). The combined filtrates were poured into Et_2O (20 mL) and aq. HCl (1 M, 20 mL). The aq. layer was extracted (Et_2O, 2 ×). The combined extracts were washed (brine, 3 ×) and dried. Evaporation and recrystallisation (EtOH) gave **37b** (2.50 g, 50%) as yellow needles: mp 112-113ºC (lit.[17] 117-118ºC); ^{1}H NMR ($CDCl_3$) (enol) δ 2.46 (6 H, s, 2 × Me), 6.84 (1 H, s, CH), 7.31 (4 H, d, J = 8.0 Hz, 2 × Ph 3,5-H_2), 7.91 (4 H, d, J = 8.5 Hz, 2 × Ph 2,6-H_2); ^{13}C NMR ($CDCl_3$) δ 21.65 (2 × Me), 92.50 (CH), 127.18 (2 × Ph 2,6-C_2), 129.39 (2 × Ph 3,5-C_2), 132.94 (2 × Ph 1-C), 143.11 (2 × Ph 4-C), 185.50 (C=O, C-OH); MS *m/z* 527.2193 $(2\ M + Na)^+$ ($C_{34}H_{32}NaO_4$ requires 527.2188), 275.1055 $(M + Na)^+$ ($C_{17}H_{16}NaO_2$ requires 275.1043).

1,3-Bis(4-methoxyphenyl)propane-1,3-dione (37c). Methyl 4-methoxybenzoate was treated with 4-methoxy-1-acetylbenzene and NaH, as for the synthesis of **37b**, to give **37c** (46%) as an off-white powder: mp 110-111ºC (lit.[18] 111.5-113.5ºC); ^{1}H NMR ($CDCl_3$) (enol form) δ 3.90 (6 H, s, 2 × Me), 6.76 (1 H, s, =CH), 6.99 (4 H, d, J = 8.5 Hz, 2 × Ph 3,5-H_2), 8.01 (4 H, d, J = 9.0 Hz, 2 × Ph 2,6-H_2); ^{13}C NMR ($CDCl_3$) δ 55.49 (2 × Me), 91.50 (=CH), 113.95 (2 × Ph 3,5-C2), 128.23 (2 × Ph 1-C), 128.09 (2 × Ph 2,6-C2), 163.03 (2 × Ph 4-C), 184.63 (C=O, C-OH); MS *m/z* 591.1950 $(2\ M + Na)^+$ ($C_{34}H_{32}NaO_8$ requires 591.1984), 307.0933 $(M + Na)^+$ ($C_{17}H_{16}NaO_4$ requires 307.0941).

1,3-Bis(4-trifluoromethylphenyl)propane-1,3-dione (37d). Methyl 4-trifluoromethylbenzoate was treated with 4-trifluoromethyl-1-acetylbenzene and NaH, as for the synthesis of **37b**, to give **37d** (57%) as an off-white powder: mp 116-117ºC (lit.[19] 130ºC); ^{1}H NMR ($CDCl_3$) (enol) δ 6.91 (1 H, s, CH), 7.80 (4 H, s, 2 × Ph 3,5-H_2), 8.12 (4 H, s, 2 × Ph 2,6-H_2); ^{13}C NMR ($CDCl_3$) δ 94.15 (CH), 122.53 (2 × Ph 1-C), 124.66 (q, J = 270.8 Hz, 2× CF_3,), 125.81 (q, J = 3.5 Hz, 2 × Ph 3,5-C_2), 127.62 (2 × Ph 2,6-C_2), 134.26 (q, J = 32.8 Hz, 2 × Ph 4-C,), 184.70 (C=O, C-OH); MS *m/z* 383.0495 $(M + Na)^+$ ($C_{17}H_{10}F_6NaO_2$ requires 383.0477).

1,3-Bis(4-chlorophenyl)propane-1,3-dione (37e). Methyl 4-chlorobenzoate was treated with 4-chloro-1-acetylbenzene and NaH, as for the synthesis of **37b**, to give **37e** (68%) as a pale pink plates: mp 130-131ºC (lit.[20] 158-159ºC); ^{1}H NMR ($CDCl_3$) (enol) δ 6.70 (1 H, s, CH), 7.40 (4 H, d, J = 8.5 Hz, 2 × Ph 3,5-H_2), 7.85 (4 H, d, J = 8.5 Hz, 2 × Ph 2,6-H_2); ^{13}C NMR ($CDCl_3$) δ 92.84 (CH), 128.49 (2 × Ph 2,6-C_2), 129.01 (2 × Ph 3,5-C_2), 133.69 (2 × Ph 1-C), 138.87 (2 × Ph 4-C), 184.71 (C=O, C-OH); MS *m/z* 316.9863 $(M + Na)^+$ ($C_{15}H_{10}{}^{35}Cl^{37}ClNaO_2$ requires 316.9923), 314.9948 $(M + Na)^+$ ($C_{15}H_{10}{}^{35}Cl_2NaO_2$ requires 314.9950).

1,3-Bis(4-bromophenyl)propane-1,3-dione (37f). Methyl 4-bromobenzoate was treated with 4-bromo-1-acetylbenzene and NaH, as for the synthesis of **37b**, to give **37f** (30%) as an off-white powder: mp 198-200ºC (lit.[21] 197-198.5ºC); ^{1}H NMR ($CDCl_3$) (enol) δ 6.70 (1 H, s, CH), 7.55 (4 H, d, J = 9.0 Hz, 2 × Ph 3,5-H_2), 7.77 (4 H, d, J = 8.5 Hz, 2 × Ph 2,6-H_2); ^{13}C NMR ($CDCl_3$) δ 92.50 (CH), 126.80 (2 × Ph 4-C)128.63 (2 × Ph 2,6-C_2), 131.99 (2 × Ph 3,5-C_2), 134.00 (2 × Ph 1-C), 184.71 (C=O, C-OH); MS *m/z* 406.8946 $(M + Na)^+$ ($C_{15}H_{10}{}^{81}Br_2NaO_2$ requires 406.8901), 404.8966 $(M + Na)^+$ ($C_{15}H_{10}{}^{79}Br^{81}BrNaO_2$ requires 404.8920), 402.8960 $(M + Na)^+$ ($C_{15}H_{10}{}^{79}Br_2NaO_2$).

1,3-Di(pyridin-4-yl)propane-1,3-dione (37l). NaH (1.00 g, 25 mmol, 60% in oil) was washed free from oil with dry hexane (10 mL) at 0ºC under Ar. Dry THF (30 mL) was added. Methyl pyridine-4-carboxylate (1.51 g, 11 mmol) in dry THF (10 mL) and 4-acetylpyridine (1.21 g, 10 mmol) in dry THF (10 mL) at 0ºC under Ar were added. The suspension was stirred under reflux for 16 h. The cooled mixture was filtered (Celite®). The filtrate was poured into Et_2O and water. Aq. HCl (9 M) was added to pH 4. The precipitate was collected and was washed (petroleum ether) to give **37l** (960 mg, 42%) as pale buff needles: mp 158-159ºC (lit.[22] 156-157ºC); ^{1}H NMR (enol) δ 7.77 (1 H, s, CH), 8.34 (4 H, d, J = 5.0 Hz, 2 × pyridine 3,5-H_2), 9.01 (4 H, d, J = 5.6 Hz, 2 × pyridine 2,6-H_2); ^{13}C NMR δ 97.50 (CH), 121.84 (2 × pyridine 3,5-C_2), 144.00 (2 × pyridine 4-C), 148.68 (2 × pyridine 2,6-C_2), 184.0 (C=O, C-OH); MS *m/z* 227.0826 $(M + H)^+$ ($C_{13}H_{11}N_2O_2$ requires 227.0815).

4-Phenylethynylbenzonitrile (42j). CuI (52 mg, 0.3 mmol), $(Ph_3P)_4Pd$ (162 mg, 0.14 mmol), Na ascorbate (33 mg, 0.16 mmol) and **42f** (500 mg, 2.75 mmol) were placed in a flask, which was degassed and filled with Ar. $Pr^i{}_2NH$ (5 mL) and THF (10 mL) were added. The mixture was stirred at 40°C for 30 min. PhC≡CH **21a** (281 mg, 2.75 mmol) was added and the mixture was stirred at 40°C for 16 h. Evaporation and chromatography (petroleum ether / EtOAc 199:1 → 99:1) gave **42j** (480 mg, 87%) as an off-white powder: mp 84-86ºC (lit.[3] mp 78-79ºC); ^{1}H NMR ($CDCl_3$) d 7.33-7.41 (3 H, m, Ph 3,4,5-H_3), 7.50-7.56 (2 H, m, Ph 2,6-H_2), 7.59-7.65 (NCPh 2,3,5,6-H_4); ^{13}C NMR ($CDCl_3$) d 87.67 (ethyne 1-C), 93.72 (ethyne 2-C), 111.39 (C≡N), 118.53 (NCPh 1-C), 122.15 (Ph 1-C), 128.19 (NCPh 4-C), 128.47 (Ph 3,5-C_2), 129.10 (Ph 4-C), 131.75 (Ph 2,6-C_2), 132.02 (NCPh 2,6-C_2), 132.03 (NCPh 3,5-C_2).

N-Methoxy-4-methylbenzimidamide (43b). 4-Methylbenzonitrile **42b** (234 mg, 2.0 mmol) in MeOH (10 mL) was stirred with $MeONH_2$.HCl (167 mg, 2.0 mmol) and Na_2CO_3 (212 mg, 2.0 mmol) in water (5 mL) for 24 h. $MeONH_2$.HCl (83.5 mg, 1.0 mmol) was added and the mixture was stirred for 2 d. The mixture was filtered. The evaporation residue, in CH_2Cl_2, was dried. Evaporation and recrystallisation ($CHCl_3$ / petroleum ether) gave **43b** (10 mg, 3%) as a white powder: mp 89-91°C (lit.[23] 85°C); ^{1}H NMR (CD_3OD) δ 2.43 (3 H, s, PhMe), 3.89 (3 H, s, OMe), 7.27 (2 H, d, J = 8.2 Hz, Ph 3,5-H_2), 7.59 (2 H, d, J = 8.2 Hz, Ph 2,6-H_2); ^{13}C NMR ($CDCl_3$) δ 21.82 (PhMe), 61.39 (OMe), 125.71 (2,6-C_2), 129.28 (3,5-C_2); MS *m/z* 165.1036 $(M + H)^+$ ($C_9H_{13}N_2O$ requires 165.1028).

N-Methoxy-4-trifluoromethylbenzimidamide (43d). Compound **42d** (342 mg, 2.0 mmol) in MeOH (5 mL) was added to $MeONH_2$.HCl (167 mg, 2.0 mmol) and Na_2CO_3 (212 mg, 2.0 mmol) in water (5 mL). The mixture was sonicated at 55°C for 30 min, then stirring continued at 20°C for 20 h. $MeONH_2$.HCl (83.5 mg, 1.0 mmol) was added and the mixture was stirred at 25°C for 24 h. The mixture was filtered. The evaporation residue, in CH_2Cl_2, was dried. Evaporation and recrystallisation ($CHCl_3$ / petroleum ether) gave **43d** (85 mg, 20%) as a white powder: mp 92-94°C; ^{1}H NMR (CD_3OD) δ 3.95 (3 H, s, Me), 7.76 (2 H, d, J = 8.7 Hz, Ph 3,5-H_2), 7.90 (2 H, d, J = 8.8 Hz, Ph 2,6-H_2), 13.99 (2 H, br, NH_2); ^{13}C NMR ($CDCl_3$) δ

125.61 (3,5-C_2), 127.32 (1-C), 129.24 (2,6-C_2), 139.99 (4-C), 152.72 (C=N); MS *m/z* 219.0730 $(M + H)^+$ ($C_9H_{10}FN_2O$ requires 219.0745).

N-Hydroxy-4-methylbenzimidamide (44b). 4-Methylbenzonitrile **42b** (940 mg, 8.0 mmol) in EtOH (30 mL) was added to $NH_2OH.HCl$ (3.34 g, 48 mmol) and $NaHCO_3$ (2.54 g, 24 mmol) in water (30 mL) and the mixture was boiled under reflux for 3 h. The EtOH was evaporated and the residue was poured into water. The precipitate was collected, washed (water) and dried to give **44b** (940 mg, 78%) as a white powder: mp 138-139°C (lit.[24] 136-137°C); ^{1}H NMR δ 2.37 (3 H, s, Me), 5.77 (2 H, br, NH_2), 7.22 (2H, d, *J* = 8.0 Hz, Ph 3,5-H_2), 7.61 (2 H, d, *J* = 8.0 Hz, Ph 2,6-H_2), 9.55 (1H, s, OH); ^{13}C NMR δ 20.78 (Me), 125.24 (2,6-C_2), 128.60 (3,5-C_2), 130.55 (1-C), 138.21 (4-C), 150.74 (C=N); MS *m/z* 151.0888 $(M + H)^+$ ($C_8H_{11}N_2O$ requires 151.0871).

N-Hydroxy-4-trifluoromethylbenzimidamide (44d). Compound **44d** was prepared as previously described.[25]

4-Chloro-N-hydroxybenzimidamide (44e). Compound **44e** was prepared as previously described.[25]

4-Bromo-N-hydroxybenzimidamide (44f). 4-Bromobenzonitrile **42f** was treated with $NH_2OH.HCl$ and $NaHCO_3$, as for the synthesis of **44b**, to give **44f** (90%) as a white powder: mp 140-141°C (lit.[26] 139-140°C); ^{1}H NMR δ 5.90 (2 H, br, NH_2), 7.60 (2 H, d, *J* = 8.8 Hz, Ph 3,5-H_2), 7.67 (2 H, d, *J* = 8.8 Hz, Ph 2,6-H_2), 9.77 (1 H, s, OH); ^{13}C NMR (HSQC / HMBC) δ 122.06 (4-C), 127.39 (3,5-C_2), 131.02 (2,6-C_2), 132.56 (1-C), 149.97 (C=N); MS *m/z* 216.9792 $(M + H)^+$ ($C_7H_8{}^{81}BrN_2O$ requires 216.9780), 214.9814 $(M + H)^+$ ($C_7H_8{}^{79}BrN_2O$ requires 214.9820).

4-Amino-N-hydroxybenzimidamide (44g). 4-Aminobenzonitrile **42g** (472 mg, 4.0 mmol) in EtOH (15 mL) was added to $NH_2OH.HCl$ (1.67 g, 24 mmol) and $NaHCO_3$ (1.27 g, 12 mmol) in water (15 mL). The mixture boiled under reflux for 8 h and cooled. The EtOH was evaporated. The residue was poured into water and extracted (EtOAc, 3 ×). The combined extracts were dried. Evaporation gave **44g** (90 mg, 15%) as a white powder: mp 157-158°C (lit.[27] 166-168°C); ^{1}H NMR δ 5.30 (2 H, br, NH_2), 5.62 (2 H, br, NH_2), 6.57 (2 H, d, *J* = 8.6 Hz, Ph 3,5-H_2), 7.38 (2 H, d, *J* = 8.6 Hz, Ph 2,6-H_2), 9.25 (1 H, s, OH); ^{13}C NMR ($CDCl_3$) δ 113.04 (3,5-C_2), 120.36 (1-C), 126.31 (2,6-C_2), 149.57 (4-C), 151.49 (C=N); MS *m/z* 174.0649 $(M + Na)^+$ ($C_7H_9N_3NaO$ requires 174.0643), 152.0853 $(M + H)^+$ ($C_7H_{10}N_3O$ requires 152.0824).

N-Hydroxy-4-nitrobenzamidine (44k). 4-Nitrobenzonitrile **42k** was treated with $NH_2OH.HCl$ and $NaHCO_3$, as for the synthesis of **44b**, to give **44k** (97%) as a white powder: mp 174-176°C (lit.[28] 176°C); ^{1}H NMR δ 4.62 (2 H, br, NH_2), 7.95 (2 H, d, *J* = 8.7 Hz, Ph 2,6-H_2), 8.32 (2 H, d, *J* = 8.7 Hz, Ph 3,5-H_2); ^{13}C NMR δ 124.53 (3,5-C_2), 128.19 (2,6-C_2), 137.00 (1-C), 149.00 (4-C), 163.00 (C=N); MS *m/z* 182.0562 $(M + H)^+$ ($C_7H_8N_3O_3$ requires 182.0566).

N-Hydroxypyridine-4-carboximidamide (44l). 4-Cyanopyridine **42l** was treated with $NH_2OH.HCl$ and $NaHCO_3$, as for the synthesis of **44b**, to give **44l** (83%) as a white powder: mp 181-184°C (lit.[29] 178-179°C); ^{1}H NMR ($CDCl_3$) δ 6.04 (2 H, br, NH_2), 7.69 (2 H, d, *J* = 4.6 Hz, 3,5-H_2), 8.62 (2 H, d, *J* = 4.8 Hz, 2,6-H_2), 10.08 (1 H, s, OH); ^{13}C NMR ($CDCl_3$) δ 121.9 (3,5-C_2), 143.07 (4-C), 150.37 (2,6-C_2), 152.22 (C=N); MS *m/z* 138.0683 $(M + H)^+$ ($C_6H_8N_3O$ requires 138.0667).

4-Methylbenzimidamide (45b). Compound **44b** (150 mg, 1.0 mmol) was boiled under reflux with $HCOONH_4$ (403 mg, 6.3 mmol) and Pd/C (10%, 150 mg) in AcOH (5 mL) for 4 d under Ar. The cooled mixture was filtered (Celite®). Aq. NaOH (1.0 M, 20 mL) was added to the evaporation residue and the mixture was extracted (EtOAc, 3 ×). Drying and evaporation gave **44b** (82 mg, 61%) as a white powder: mp 53-55°C (lit.[30] 68°C); ^{1}H NMR δ 2.42 (3 H, s, Me), 6.72 (3 H, br, NH + NH_2), 7.25 (2 H, d, J = 8.4 Hz, Ph 3,5-H_2), 7.72 (2 H, d, J = 8.3 Hz, Ph 2,6-H_2); ^{13}C NMR δ 20.08 (Me), 126.46 (2,6-C_2), 128.56 (3,5-C_2), 133.16 (1-C), 139.44 (4-C), 162.57 (C=N); MS *m/z* 135.1018 $(M + H)^+$ ($C_8H_{11}N_2$ requires 135.0922).

4-Trifluoromethylbenzimidamide (45d). Compound **45d** was prepared as previously described.[25]

4-Chlorobenzimidamide (45e). Compound **45e** was prepared as previously described.[25]

4-Bromobenzimidamide (45f). Compound **44f** was treated with $HCOONH_4$ and Pt/C, as for the synthesis of **45e**, to give **45f** (94 mg, 68%) as a white powder: mp 257-259°C (lit.[31] 258.5-259.5°C); ^{1}H NMR δ 7.51 (2 H, br, NH_2), 7.53 (2 H, d, J = 7.6 Hz, 3,5-H_2), 7.79 (2 H, d, J = 7.2 Hz, 2,6-H_2), 7.93 (1 H, br, NH); ^{13}C NMR δ 126.73 (3,5-C_2), 128.22 (2,6-C_2), 129.59 (4-C), 131.20 (1-C), 166.90 (C=N); MS *m/z* 200.9851 $(M + H)^+$ ($C_7H_8{}^{81}BrN_2$ requires 200.9851), 198.9877 $(M + H)^+$ ($C_7H_8{}^{79}BrN_2$ requires 198.9871).

4-Aminobenzimidamide (45g). Compound **44g** (151 mg, 1.0 mmol) was stirred under reflux in AcOH (5 mL) with Pd/C (1%, 362 mg) and $HCOONH_4$ (800 mg, 12.6 mmol) for 4 d, before being cooled and filtered (Celite®). The evaporation residue was basified with aq. NaOH (5 M, 20 mL) and extracted thrice with EtOAc. Drying and evaporation gave **45g** (80 mg, 59%) as a white powder: mp 200-201°C (lit.[32] 171°C); ^{1}H NMR δ 6.70 (3 H, br, NH & NH_2), 7.35 (2 H, br, NH_2), 7.66 (2 H, d, J = 8.6 Hz, Ph 3,5-H_2), 7.73 (2 H, d, J = 8.6 Hz, Ph 2,6-H_2); ^{13}C NMR δ 117.80 (3,5-C_2), 127.21 (2,6-C_2), 133.0 (1-C), 140.0 (4-C), 152.0 (C=N); MS *m/z* 136.0898 $(M + H)^+$ ($C_7H_{10}N_3$ requires 136.0875).

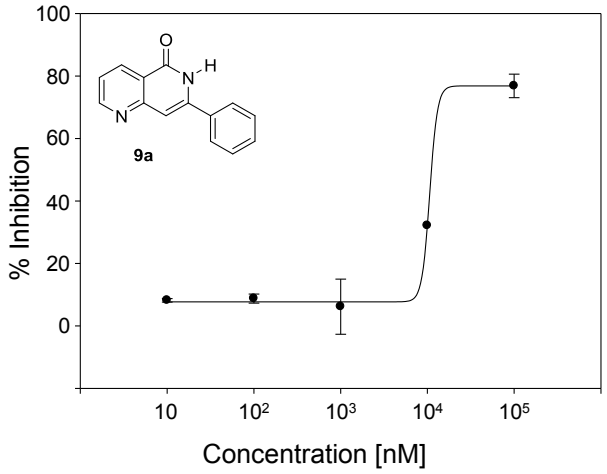
4-Phenylethynylbenzimidamide (45j). NaOMe (134 mg, 2.5 mmol) was stirred under reflux for 2 h with **44j** (480 mg, 2.36 mmol) in dry MeOH (15 mL). NH_4Cl (278 mg, 5.2 mmol) was added and stirring under reflux continued for 2 h. Evaporation and recrystallisation (water) gave **45j** (355 mg, 68%) as an off-white powder: mp 90-91ºC; ^{1}H NMR d 7.51-7.54 (3 H, m, Ph 3,4,5-H_3), 7.67 (2 H, m, Ph 2,6-H_2), 7.81 (2 H, m, amidine Ph 2,6-H_2), 7.89 (1 H, br, NH), 7.97 (2 H, m, amidine-Ph 3,5-H_2), 9.06 (1 H, br, NH), 9.45 (1 H, br, NH); ^{13}C NMR d 88.30 (ethyne 1-C), 93.60 (ethyne 2-C), 111.05 (amidine Ph 1-C)118.44 (amidine Ph 4-C), 121.39 (Ph 1-C), 128.88 (Ph 3,4,5-C_3), 129.55 (Ph 4-C), 131.63 (Ph 2,6-C_2), 132.15 (amidine Ph 3,5-C_2), 132.62 (amidine Ph 2,6-C_2); MS *m/z* 242 $(M + Na)^+$, 221.1090 $(M + H)^+$ ($C_{15}H_{13}N_2$ requires 221.1073).

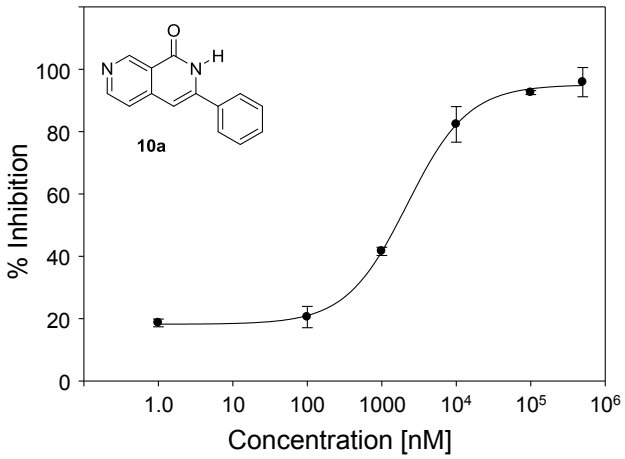
Pyridine-4-carboximidamide (45l). Compound **44l** (137 mg, 1.0 mmol) was boiled under reflux with Pd/C (1%, 150 mg) and $HCOONH_4$ (400 mg, 6.3 mmol) in AcOH (5 mL) for 4 d. The suspension was filtered (Celite®). The evaporation residue was basified with aq. NaOH (5 M, 20 mL) and extracted (EtOAc, 3 ×). Evaporation and drying gave **45l** (30.5 mg, 25%) as a white powder: mp >200°C (decomp.) (lit.[33] 235-238°C); ^{1}H NMR δ 7.78 (2 H, d, J = 5.5 Hz, 3,5-H_2), 8.87 (2 H, d, J = 5.0 Hz, 2,6-H_2), 9.52 (3 H, br, NH and NH_2); ^{13}C NMR δ 121.39 (3,5-C_2), 141.24 (4-C), 150.24 (2,6-C_2), 166.38 (C=N); MS *m/z* 122.0710 $(M + H)^+$ ($C_6H_8N_3$ requires 122.0718).

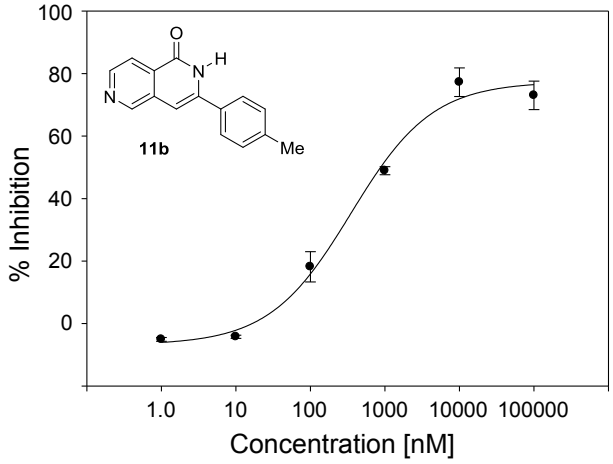
Data collection and refinement statistics for the tankyrase-2 crystal structures

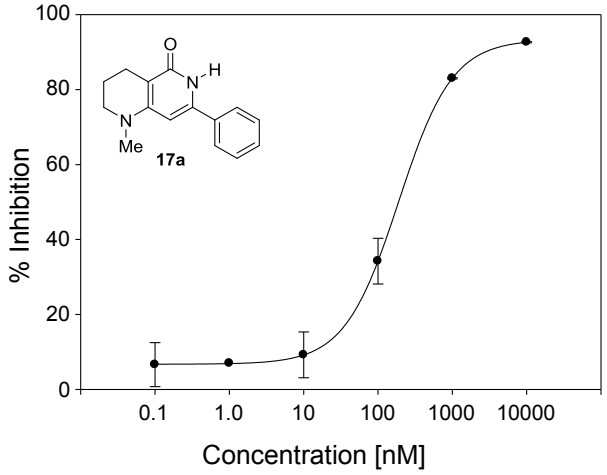
Compound	**17a**	**12b**
PDB code	**4W5I**	**4UX4**
Data		
Beam line	Diamond I04-1	Diamond I04-1
Wavelength (Å)	0.92000	0.92000
Space group	$C222_1$	$C222_1$
Cell dimensions		
a, b, c (Å)	91.55, 98.12, 119.22	91.56, 97.89, 118.47
Resolution (Å)	30-1.95 (2.00-1.95)	50-1.80 (1.85-1.80)
R_{merge}	13.2 (86.4)	6.3 (83.6)
I / σI	9.87 (2.15)	18.80 (2.17)
Completeness (%)	99.8 (100)	99.9 (100)
Redundancy	6.7 (6.9)	6.8 (7.0)
Refinement		
R_{work} / R_{free}	0.162/0.200	0.162/0.198
B-factors		
Protein	27.2	28.3
Inhibitor	18.1	34.3
R.m.s.d.		
Bond lengths (Å)	0.011	0.012
Bond angles (°)	1.4	1.5
Ramachandran plot (%)		
Favoured regions	99.3	99.3
Additionally allowed regions	0.7	0.7

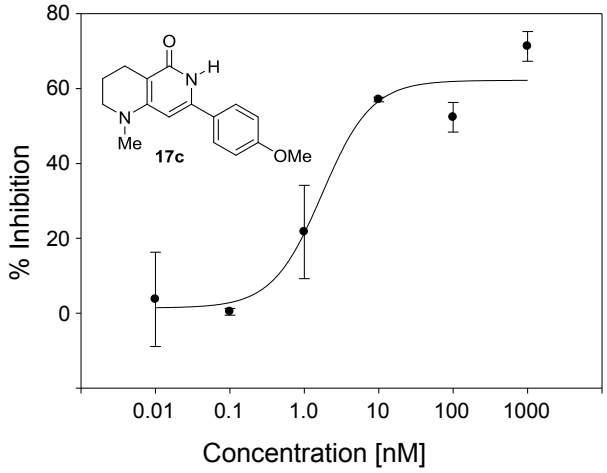
Examples of concentration-inhibition graphs for inhibition of TNKS-1

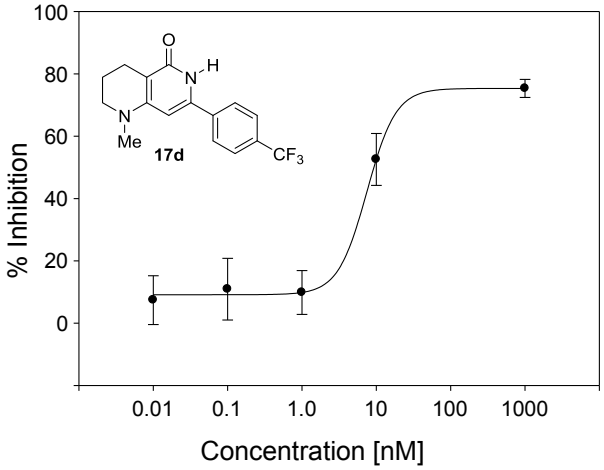


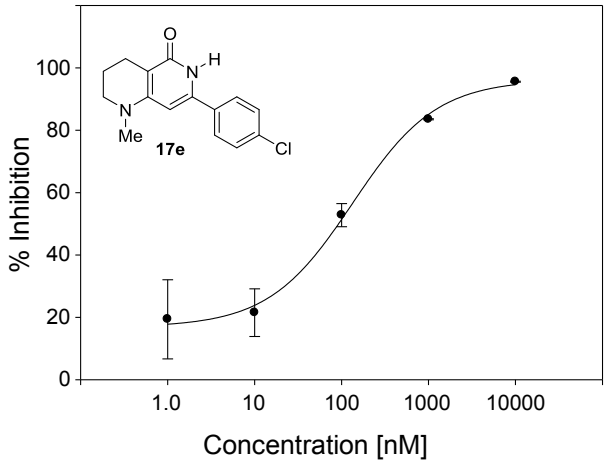








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100
1000
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Concentration [nM]
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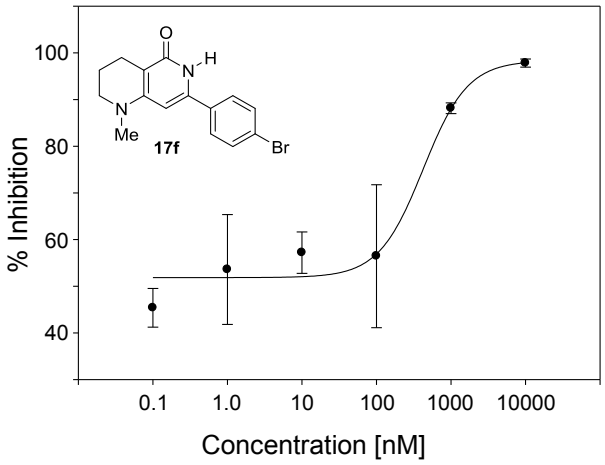
N
H
N
Me
17e
Cl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Concentration [nM]
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H
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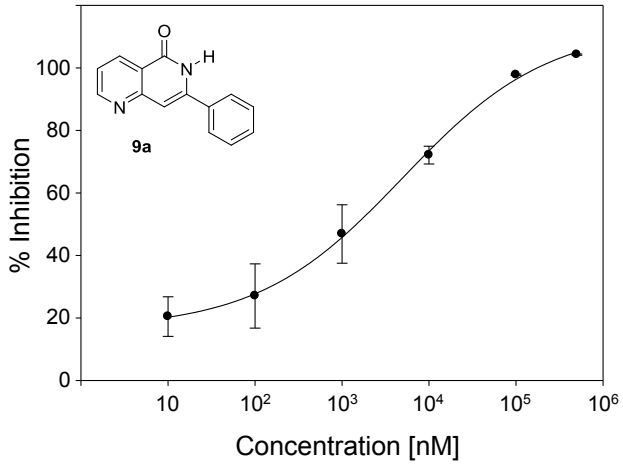
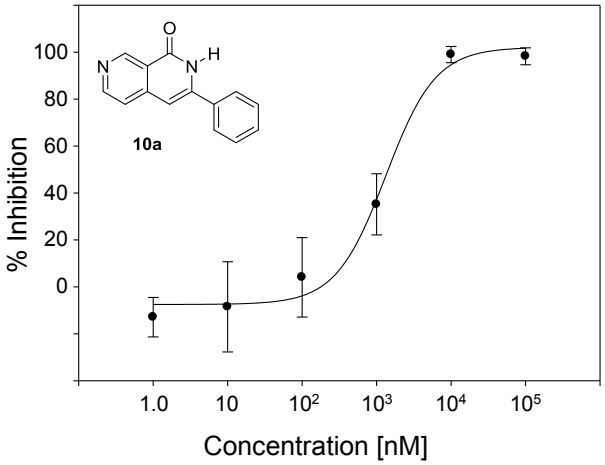
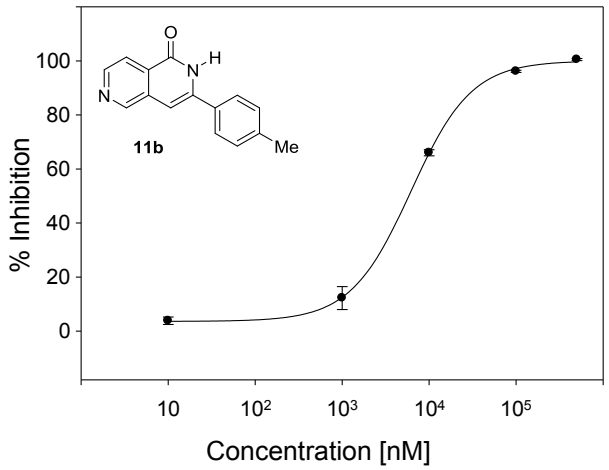
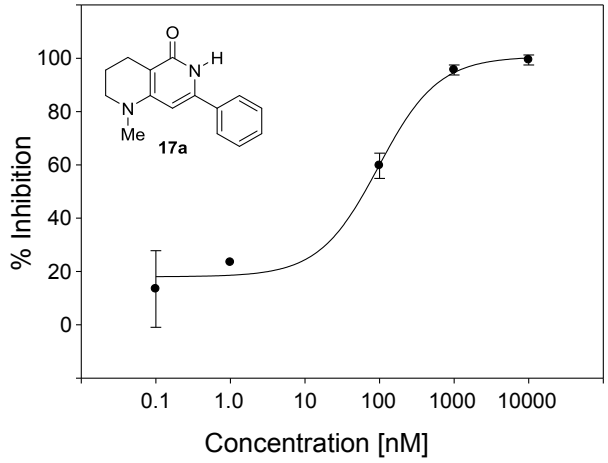
17f
Br

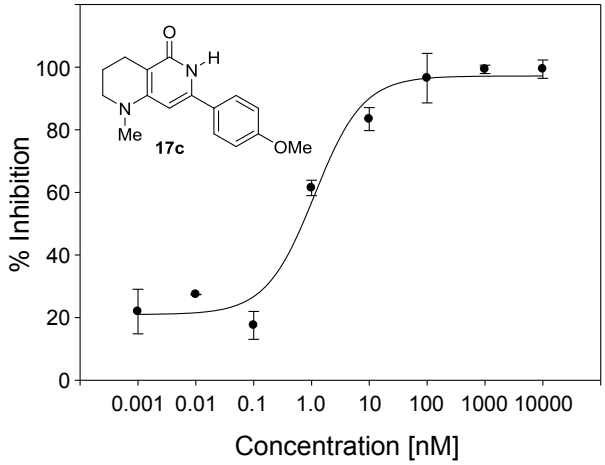
Examples of concentration-inhibition graphs for inhibition of TNKS-2

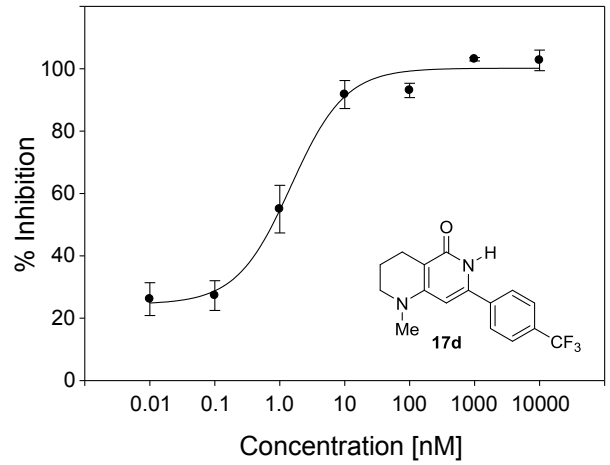


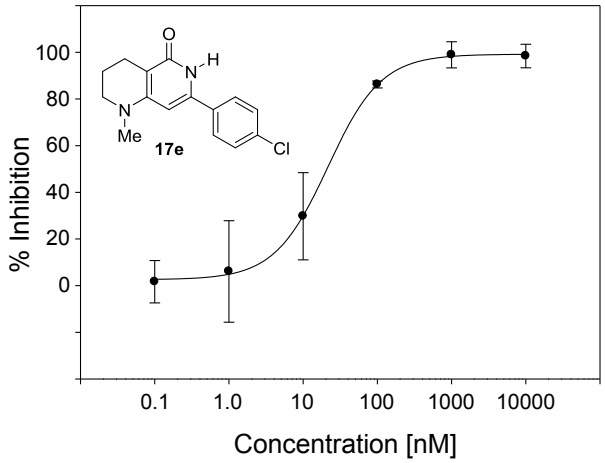


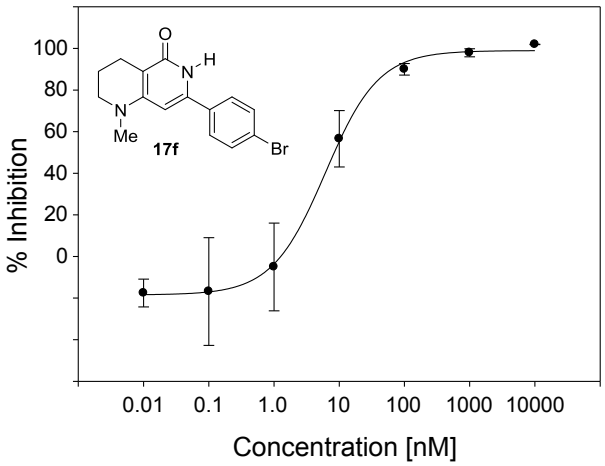




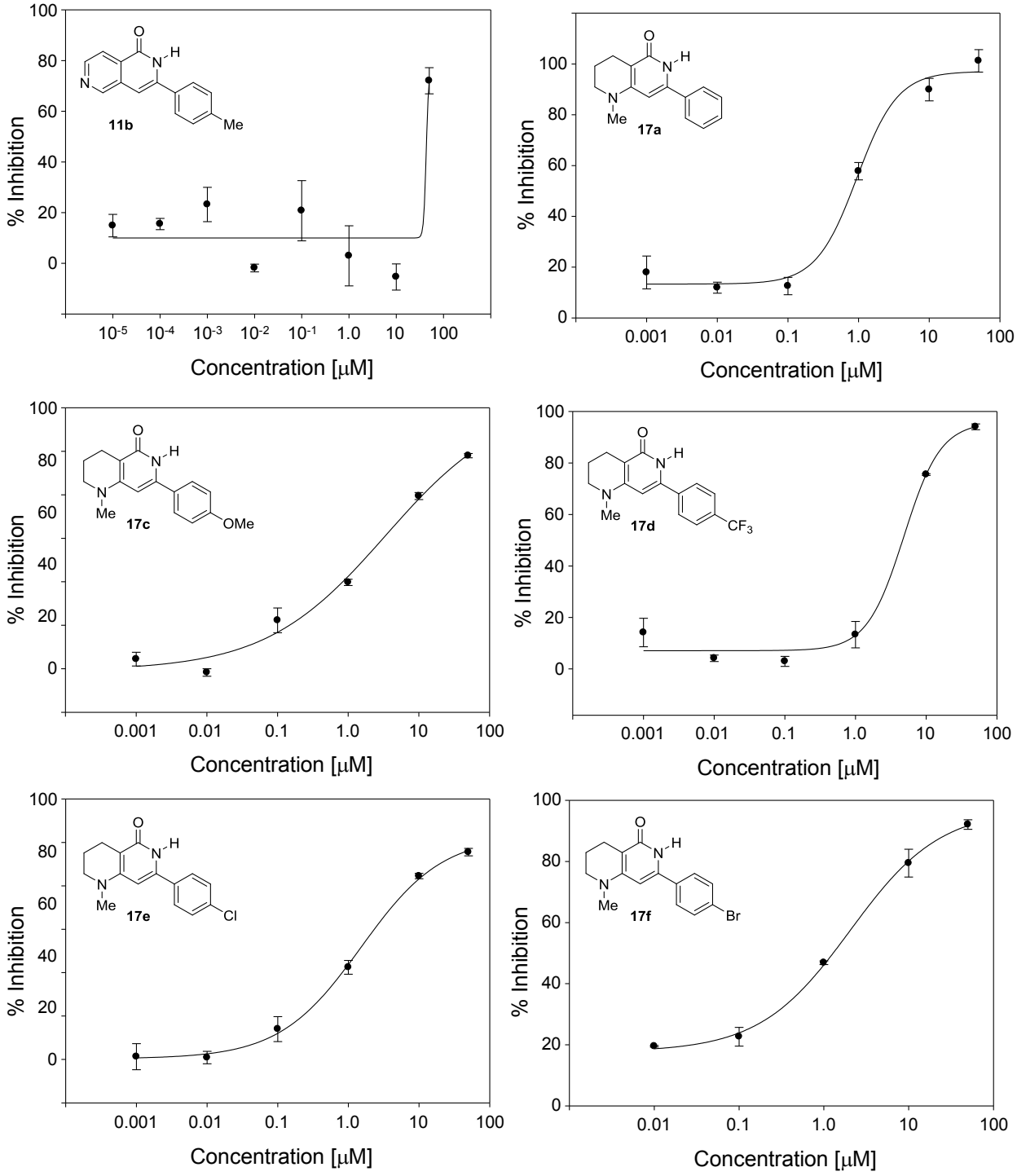





% Inhibition
100
80
60
40
20
0
0.1
1.0
10
100
1000
10000
Concentration [nM]
O
N
H
N
Me
Cl
17e


% Inhibition
100
80
60
40
20
0
0.01
0.1
1.0
10
100
1000
10000
Concentration [nM]
O
N
H
N
Me
Br
17f

Examples of concentration-inhibition graphs for inhibition of PARP-1



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